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Correlation of Airway Resistance with Forced Random Noise Resistance Parameters

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16. ABSTRACT
The correlation between airway resistance (RAW) measured in a plethysmograph and three respiratory resistance parameters measured by forced random noise was evaluated. Forced random noise resistance parameters were the average resistance between 5 and 9 Hz (R_{5-9}), the average resistance between 20 and 24 Hz (R_{20-24}), and the extrapolated resistance at 1 Hz (R_1). We studied 22 healthy, nonsmoking subjects, 10 of whom had a history suggesting childhood asthma. Serial measurements were made after inhalation of aerosols containing increasing concentrations of methacholine to obtain increasing concentrations of methacholine to obtain data in various stages of bronchoconstriction. There was a broad range of responsiveness to methacholine; the ratio of the peak to base-line values of Raw ranged from 1.1 to 6.3. R_1, R_{5-9}, and R_{20-24} were related to Raw by linear regression analysis. R_1, and R_{5-9} showed excellent correlation with Raw (r=0.93 and r-0.91, respectively); R_{20-24} showed much poorer correlation (r=0.62). The slopes of the regression equations for R_1 and R_{5-9} were 1.56 and 0.51, respectively; thus neither provided an exact measure of Raw. The data appear to be consistent with a model in which most of the methacholine-induced increase in resistance occurred in the peripheral airways and only a small fraction in the central airway.

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Correlation of airway resistance with forced random noise resistance parameters

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PIMMEL, R. L., J. M. FULLTON, J. F. GINSBERG, M. J. HAZUCHA, E. D. HAAK, W. F. McDONNELL, AND P. A. BROMBERG. *Correlation of airway resistance with forced random noise resistance parameters.* J. Appl. Physiol.: Respirat. Environ. Exercise Physiol. 51(1): 33–39, 1981.—The correlation between airway resistance (Raw) measured in a plethysmograph and three respiratory resistance parameters measured by forced random noise was evaluated. Forced random noise resistance parameters were the average resistance between 5 and 9 Hz (R_{5-9}), the average resistance between 20 and 24 Hz (R_{20-24}), and the extrapolated resistance at 1 Hz (R_1). We studied 22 healthy, nonsmoking subjects, 10 of whom had a history suggesting childhood asthma. Serial measurements were made after inhalation of aerosols containing increasing concentrations of methacholine to obtain data in various stages of bronchoconstriction. There was a broad range of responsiveness to methacholine; the ratio of the peak to base-line values of Raw ranged from 1.1 to 6.3. R_1, R_{5-9}, and R_{20-24} were related to Raw by linear regression analysis. R_1 and R_{5-9} showed excellent correlation with Raw ($r = 0.93$ and $r = 0.91$, respectively); R_{20-24} showed much poorer correlation ($r = 0.62$). The slopes of the regression equations for R_1 and R_{5-9} were 1.56 and 0.51, respectively; thus neither provided an exact measure of Raw. The data appear to be consistent with a model in which most of the methacholine-induced increase in resistance occurred in the peripheral airways and only a small fraction in the central airway.

methacholine challenge; frequency dependence of resistance; respiratory mechanics, respiratory models

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SEVERAL REPORTS have described methods for measuring respiratory resistance parameters using forced random small-amplitude pressure and flow signals, referred to as forced random noise (7, 11, 15). This approach has two advantages over the more conventional methods using either a body plethysmograph or an esophageal balloon (1, 10). First, it requires less subject cooperation, as the only requirement is that subjects breathe quietly through a mouthpiece while supporting their cheeks. Second, it rapidly provides measures of resistance as a function of frequency, which may be used to partition resistance into central and peripheral components (13, 14, 16). The purpose of the present study was to examine the correlation between airway resistance measured in a plethysmograph and three resistance parameters measured by forced random noise. To obtain data in various stages of bronchoconstriction, we made serial measurements after subjects inhaled aerosols containing increasing concentrations of methacholine. The results of this study indicate that several forced random noise resistance parameters were correlated with Raw and that this technique may provide data which can be used to localize mechanical changes.

METHODS

Measurements were made on 22 nonsmoking male subjects ranging in age from 18 to 35 yr. Ten subjects had a history suggesting childhood asthma. None of the subjects was taking any medication for respiratory illness, and all were asymptomatic at the time of the study. All subjects had a forced vital capacity (FVC) greater than 70% of their predicted value and a ratio of forced expiratory volume at 1.0 s ($FEV_{1.0}$) to FVC greater than 0.70. All had been involved in an extensive study of respiratory function and were trained in all maneuvers before data for the present study were recorded.

During this study, we measured airway resistance (Raw) using standard plethysmographic techniques (1) and three other resistance parameters using a forced random noise technique (7, 15). Raw was measured with a constant-volume plethysmograph. During this measurement, subjects were prompted to pant at a rate of 1.5 Hz by a recording of simulated breath sounds and with peak flow rates of 1.0 $l \cdot s^{-1}$ by an oscilloscopic display of the flow signal. Data in the range of ± 0.5 $l \cdot s^{-1}$ from four to six panting cycles were averaged to obtain Raw.

Forced random noise data were obtained immediately after the plethysmographic measurement by a technique previously described (7, 15). Briefly, subjects were connected by a mouthpiece to a loudspeaker-transducer system. The loudspeaker was excited by a random electronic signal with a bandwidth of 5–35 Hz. With a noseclip in place, subjects supported their cheeks and breathed tidally while a 75-s record of the random pressure and flow signals was recorded on magnetic tape.

Recorded random pressure and flow signals were analyzed off-line by spectral analysis techniques (15). An arbitrary segment of the taped data was digitized at a rate of 512 samples/s to form 45 1-s records. A 75-s record was required, because each record was processed individually while the tape continued to run. Spectra from these 45 records were averaged and processed to obtain esti-

mates of the Thevenin, or effective, resistance (RTh) at 1-Hz intervals over the range of 5–35 Hz. The five values in the range of 5–9 Hz were averaged to provide a measure of low-frequency resistance (R_{5-9}). Similarly, the five values in the range of 20–24 Hz were averaged to provide a measure of high-frequency resistance (R_{20-24}). From each set of RTh-frequency data, the resistance at 1 Hz (R_1) was calculated by extrapolating the regression line relating the logarithm of RTh to the logarithm of frequency (13).

After two sets of base-line measurements, a sequence of measurements was made after subjects inhaled aerosolized solutions containing increasing concentrations of methacholine (acetyl β-methylcholine, Sigma Chemical, St. Louis, MO). Initial methacholine concentrations were 0.075 $mg \cdot ml^{-1}$ for subjects with any history suggesting childhood asthma and 0.31 $mg \cdot ml^{-1}$ for all other subjects. On each of seven successive exposures, methacholine concentration essentially was doubled. The final concentrations were 5.0 $mg \cdot ml^{-1}$ for subjects with a history suggesting childhood asthma and 20 $mg \cdot ml^{-1}$ for all other subjects. All measurements were completed within 7 min of each inhalation. Methacholine solutions were prepared daily from a sterile stock solution, which, in turn, was prepared weekly and stored at 4°C.

Aerosols were generated using a DeVilbiss no. 65 ultrasonic nebulizer with a series of baffles added to further narrow the distribution of particle size. The aerosol from this apparatus has been characterized using a cascade impacter, and particles have been produced with an aerodynamic mass mean diameter ranging from 1 to 1.3 μm, depending on methacholine concentration. It is believed that this size particle is deposited in the periphery of the lung. During each exposure to methacholine, subjects inhaled five 850-ml breaths. They were instructed to inspire at a normal rate and to hold their breath for 4 s after each inspiration. Subjects frequently were instructed to refrain from any deep breaths; however, their breathing patterns were not monitored.

For each of the 22 subjects, there were nine sets of resistance parameters resulting from the two base-line measurements and from the seven measurements after exposure to various methacholine-containing aerosols. The three forced random noise parameters, R_1, R_{5-9}, and R_{20-24}, were compared to plethysmographic Raw by linear regression analysis.

RESULTS

The population mean values ±SD of the base-line measurements of Raw, R_1, R_{5-9}, and R_{20-24} were 1.30 ± 0.65, 2.12 ± 1.29, 2.42 ± 0.73, and 2.70 ± 0.54 $cmH_2O \cdot l^{-1} \cdot s$, respectively. All but two subjects inhaled all seven methacholine concentrations; these two stopped after the sixth concentration because of discomfort. There was a broad range of responsiveness to methacholine, and the ratio of the peak value to the base-line values of Raw ranged from 1.1 to 6.3. In most subjects, the peak response in Raw occurred after the last methacholine dose, but a few subjects reached their peak response after the second-to-last dose.

Figure 1 shows RTh as a function of frequency at three concentrations for two subjects with different degrees of responsiveness. With *subject N007*, a normal subject, Raw increased from a base-line value of 0.80 $cmH_2O \cdot l^{-1} \cdot s$ to a value of 4.51 $cmH_2O \cdot l^{-1} \cdot s$ at the highest concentration. With *subject A051*, a subject with a history of childhood asthma, the corresponding values were 1.65 and 9.19 $cmH_2O \cdot l^{-1} \cdot s$, respectively. In the base-line measurement, RTh increased slightly with frequency in *subject N007* and was flat in *subject A051*. As the concentration of methacholine increased, changes in RTh were not uniform over the frequency spectrum. In the lower frequency range, RTh increased much more rapidly than it did in the higher frequency range. Thus, as the concentration of methacholine increased, the slopes of the curves relating RTh to frequency, which were initially flat or slightly positive, became progressively more negative.

Figure 2 gives dose-response curves for the same two subjects represented in Fig. 1. These curves show Raw, R_1, R_{5-9}, and R_{20-24} as a function of the logarithm of the methacholine concentration. At low concentrations Raw,

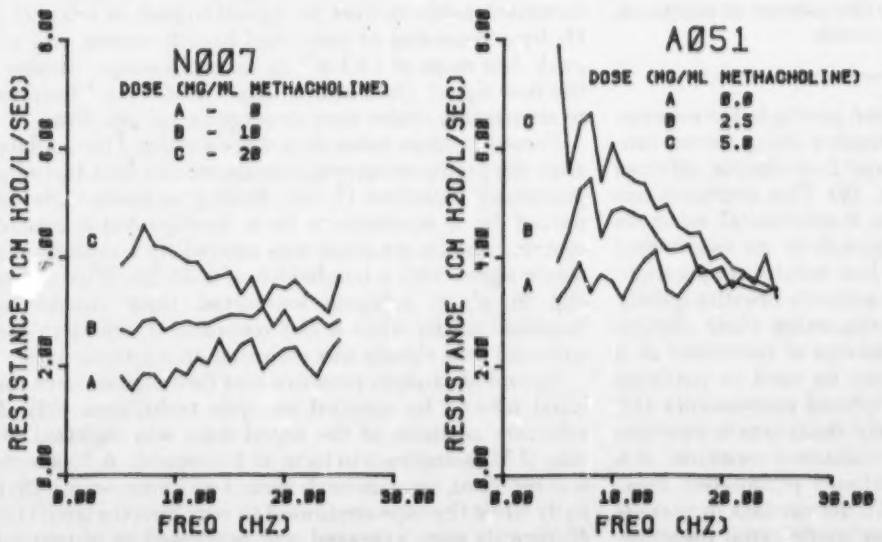

FIG. 1. Thevenin resistance as function of frequency for 2 subjects following inhalations of aerosols containing three methacholine concentrations.

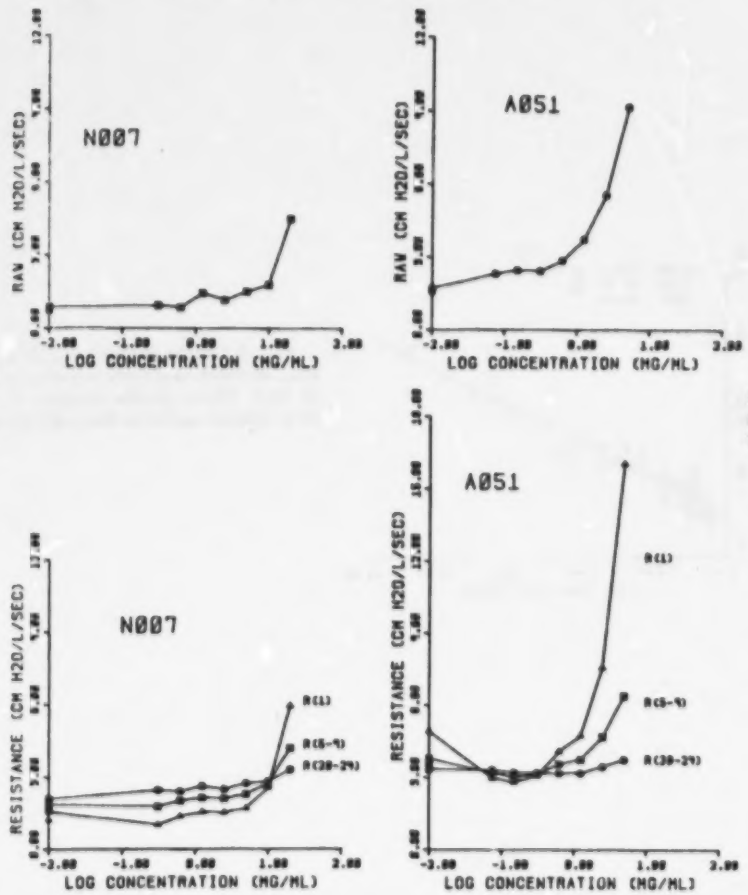

FIG. 2. Dose-response curves showing Raw, R_1, R_{5-9}, and R_{20-24} as function of methacholine concentration for same two subjects represented in Fig. 1. *Horizontal axis* is logarithmic scale.

R_1, and R_{5-9} changed slightly as the concentration was increased. However, once the concentration reached a threshold value, which varied considerably among the 22 subjects, these resistance parameters all increased markedly as the concentration was increased further. In contrast, R_{20-24} increased only slightly as methacholine concentration increased.

Figure 3 shows plots of R_1, R_{5-9}, and R_{20-24} as a function of the corresponding value of Raw; these graphs contain all the data. In contrast, the graphs in Fig. 4 have expanded scales and contain only data for which Raw was less than 3 $cmH_2O \cdot l^{-1} \cdot s$. We chose to consider this subset because it represents data from relatively normal lungs with, at most, mild induced bronchoconstriction. Linear regression lines are shown on each graph.

Although the linear regression line obtained with all R_1 and Raw data had a high correlation coefficient of 0.93, the relationship appeared to be curvilinear with a slope that increased with Raw. The existence of this curvilinear relationship was supported by the difference in the slopes for the regression line between R_1 and Raw obtained with all data, 1.56 (Fig. 3*A*), and with the subset of these data, for which Raw was less than 3 $cmH_2O \cdot l^{-1} \cdot s$, 1.03 (Fig. 4*A*). The intercept for the regression line with all data was -0.29 $cmH_2O \cdot l^{-1} \cdot s$; the corresponding value for the low-resistance subset was 0.46 $cmH_2O \cdot l^{-1} \cdot s$. These data suggest that, for the low-resistance condition, R_1 approximately equals Raw plus the constant value 0.46 $cmH_2O \cdot l^{-1} \cdot s$. As the forced random noise technique measured the sum of airway and tissue resistance; this intercept, corresponding to zero airway resistance, may be interpreted as the sum of chest wall and lung tissue resistance.

The regression line obtained with all R_{5-9} and Raw data also had a high correlation coefficient, 0.91. The relationship between these two parameters also appeared to be curvilinear; however, in contrast to R_1, the slope appeared to decrease with increasing Raw. The existence of this curvilinear relationship also was supported by the difference in the slopes of the regression lines with all data, 0.51 (Fig. 3*B*), and with the low-resistance subset, 0.72 (Fig. 4*B*).

The relationship between R_{20-24} and Raw was more curvilinear than the other two. This forced noise parameter increased with Raw up to a value of approximately 2 $cmH_2O \cdot l^{-1} \cdot s$, above which R_{20-24} appeared to increase very little with increases in Raw. The slope of the regression line with all data, 0.16, suggests that R_{20-24} changes little as Raw increased.

DISCUSSION

The forced random noise technique yields estimates of the Thevenin, or effective, resistance of the respiratory

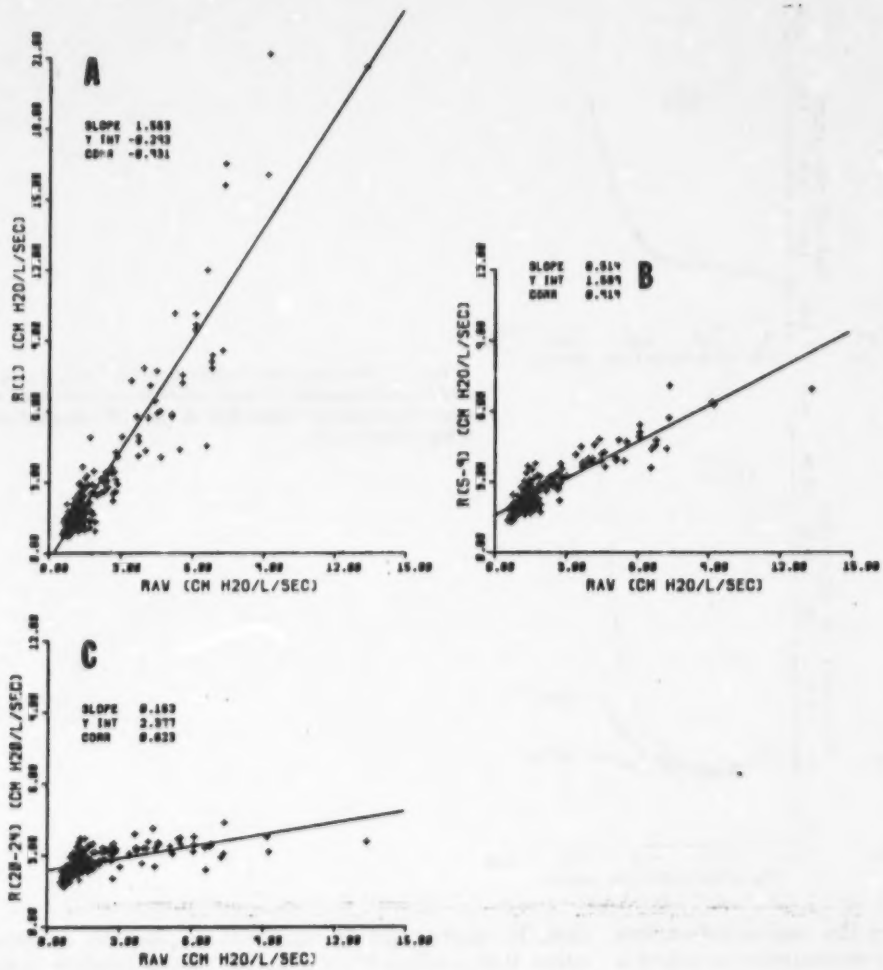

FIG. 3. Graphs showing R_1, R_{5-9}, and R_{20-24} as function of corresponding values of Raw. These graphs contain all the data. Linear regression lines are shown.

system as a function of frequency (7, 11, 15). In normal adult subjects this relationship should have a small positive slope (3, 5, 7). In asymptomatic young subjects, statistically significant differences in the ratios of low- to high-frequency RTh between normals and cigarette smokers have been reported (7, 8). In patients with obstructive lung disease, RTh decreased markedly with frequency in a curvilinear fashion (6, 7, 11). In the present study, we used aerosols containing methacholine to induce bronchoconstriction and to obtain data from lungs with various degrees of obstruction. In the base-line data, RTh was either independent of frequency or it increased slightly as frequency increased. In general, as the methacholine concentration increased, the RTh-frequency curve progressively changed from a normal configuration to one similar to that seen in obstructive lung disease. Figure 1 shows two examples of the changes that occurred as methacholine concentration increased.

The frequency dependence of resistance has been explained by models that contain parallel compartments with dissimilar time constants. The model of Otis et al. (12) assigned both compartments to the parenchyma, whereas that of Mead (9) assigned one compartment to the airway and one to the parenchyma. Michaelson et al. (11) indicated that Mead's model with an added central resistance and inertance (Fig. 5) best explained their forced random noise data. In a related study in our laboratory (2), we developed nonlinear regression analysis algorithms for estimating parameters in several linear models with parallel compartments. In this study, we found that the modified Mead model provided the best agreement with the data and the most stable estimates of resistance, compliance, and inertance parameters.

An analysis of the modified Mead model showed that if peripheral resistance (Rp) was small relative to central resistance (Rc), nominally less than 10%, and peripheral compliance (C_2) was large relative to airway compliance (C_1), then RTh was independent of frequency. In this model, frequency dependence did not result from increases in Rc. However, as Rp increased, RTh became more and more frequency dependent. Figure 6 shows a family of RTh-frequency curves obtained with central inertance (Ic) = 0.008 $cmH_2O \cdot l^{-1} \cdot s^2$, Rc = 2.0 $cmH_2O \cdot l^{-1} \cdot s$, C_1 = 0.005 $l \cdot cmH_2O^{-1}$, and C_2 = 0.1 $l \cdot cmH_2O^{-1}$. Rp was set to several values, ranging from 0.5 to 8.0 $cmH_2O \cdot l^{-1} \cdot s$, to generate the eight curves; actual values are listed in the caption of Fig. 6. With each value of Rp, it was noteworthy that the low-frequency asymptote repre-

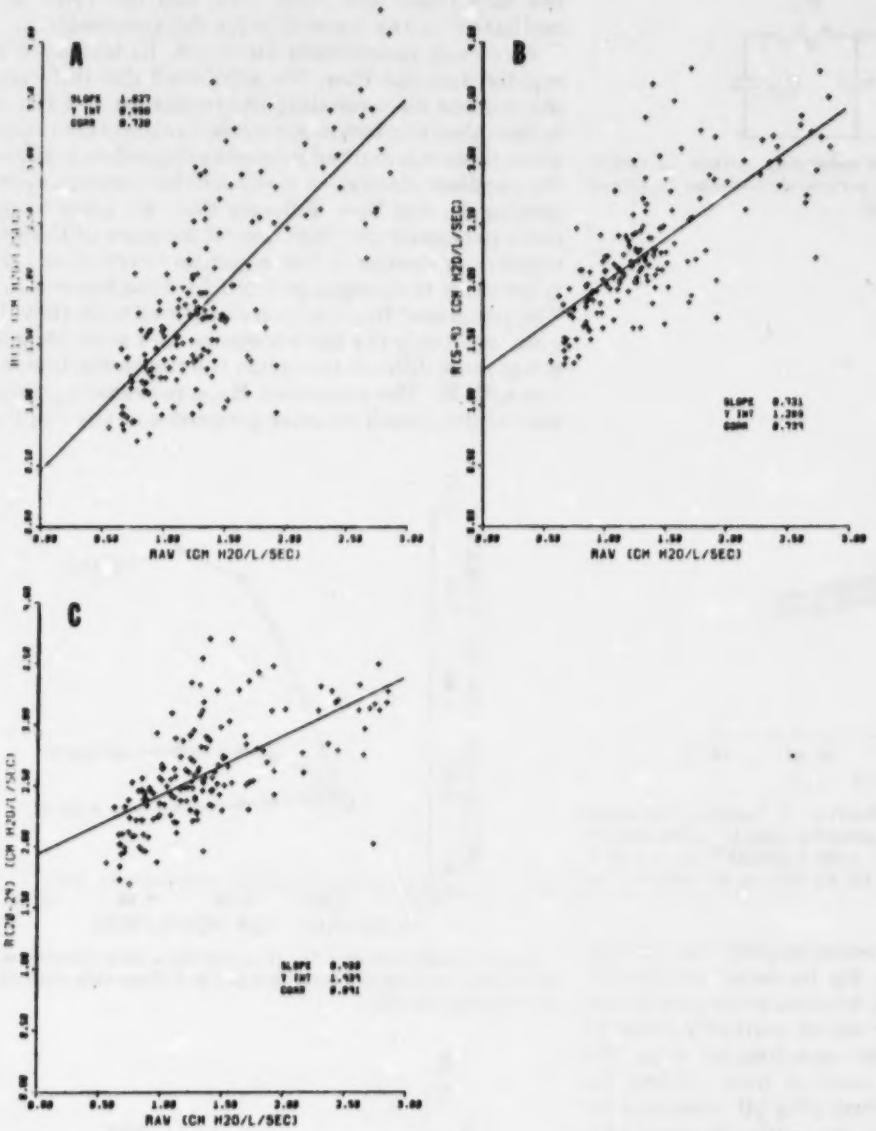

FIG. 4. Graphs showing R_1, R_{5-9}, and R_{20-24} as function of corresponding values of Raw. These graphs contain all data for which Raw was less than 3.0 $cmH_2O \cdot l^{-1} \cdot s$. Linear regression lines are shown.

sented total resistance, whereas the high-frequency asymptote approximated Rc. This family of curves was similar to those obtained experimentally during methacholine challenge (Fig. 1). This similarity suggested that inhalation of a methacholine-containing aerosol had a marked effect in the lung periphery. Although the behavior of this model agrees with the experimental data, there are other models for explaining the data, and there are alternate anatomical interpretations for the elements in the model shown in Fig. 5.

In an effort to obtain simple parameters for comparison with the more traditional plethysmographic Raw, we defined three resistance parameters. Two derived parameters, R_{5-9} and R_{20-24}, characterize the measured low- and high-frequency resistance. We chose to average five values to reduce the parameter variability that resulted from the use of random excitation. The third derived resistance parameter, R_1, represents an estimate of the RTh at 1 Hz. It was obtained by extrapolating the regression line relating the logarithms of RTh and frequency. The extrapolation was based on the previously reported mathematical relationship between the RTh and frequency in the modified Mead model (13, 16).

In order to determine how well the derived parameters R_1, R_{5-9}, and R_{20-24} correlated with the actual overall resistance (Rc + Rp), we computed values for the three derived parameters using the model data shown in Fig. 6. Resulting values for the three derived parameters are plotted as a function of Rc + Rp in Fig. 7. Assuming that changes in Rc + Rp correspond to changes in Raw makes these curves analogous to the experimental data shown in Fig. 3. For values of Rc + Rp less than approximately 5 $cmH_2O \cdot l^{-1} \cdot s$, the relationship exhibited by each parameter derived from the model data agreed with that seen in the experimental data. As Rc + Rp increased, R_1 increased at an increasing rate; R_{5-9} increased at a de-

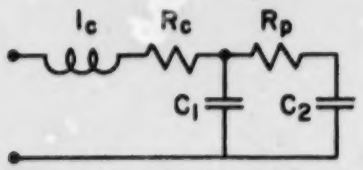

FIG. 5. Electrical circuit model of respiratory system. Ic, central inertance; Rc, central resistance; Rp, peripheral resistance; C_1, airway compliance; C_2, peripheral compliance.

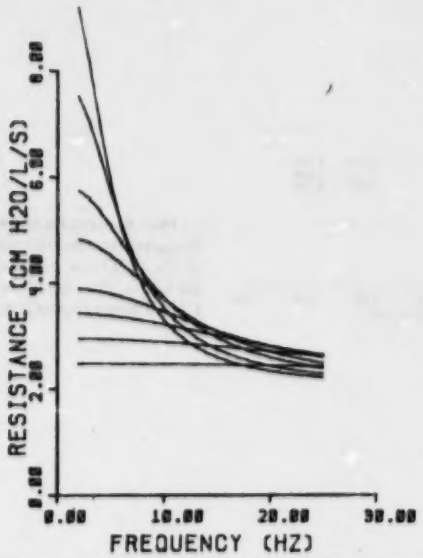

FIG. 6. Thevenin resistance as function of frequency for model shown in Fig. 5. Family of curves was generated using Ic = 0.008 $cmH_2O \cdot l^{-1} \cdot s^2$; Rc = 2.0 $cmH_2O \cdot l^{-1} \cdot s$; C_1 = 0.005 $l \cdot cmH_2O^{-1}$; C_2 = 0.10 $l \cdot cmH_2O^{-1}$; and R_p = 0.5, 1.0, 1.5, 2.0, 3.0, 4.0, 6.0, and 8.0 $cmH_2O \cdot l^{-1} \cdot s$. Abbreviations as in Fig. 5.

creasing rate; and R_{20-24} increased slightly but quickly reached a plateau. As Rc + Rp increased beyond 5.0 $cmH_2O \cdot l^{-1} \cdot s$, all three forced random noise parameters began decreasing. This latter aspect markedly deviated from the pattern seen in the experimental data. We believe that this difference resulted from holding Rc constant in the model and attributing all resistance increases to Rp. Figure 8 shows the results obtained with a model in which 25% of the resistance increase was assigned to Rc and 75% to Rp. After Rc had increased by 50% of its initial value, it was held constant, and all additional resistance increases were assigned to Rp. The curves in Fig. 8 more closely resemble the experimental data in Fig. 3 than those in Fig. 7. The fact that the major resistance changes appear peripheral is consistent with the suspected peripheral deposition of the aerosol we used in our study.

Our experimental data suggest that with normal or mildly constricted airways, R_1 provided a good estimate of the overall resistive properties. The regression line between R_1 and Raw had a slope of 1.03 (Fig. 4*A*), indicating that values of R_1 and Raw differed by a constant and that increases in R_1 and Raw were equal. In addition, the intercept of this regression line represented the total resistance when the airway resistance was zero. This intercept may be interpreted as the resistance of the lung tissue and chest wall, and the value of 0.47 $cmH_2O \cdot l^{-1} \cdot s$ was reasonable for this parameter.

As airway constriction increased, R_1 increased more rapidly than did Raw. We attributed this difference to our method for estimating the resistance at 1 Hz, as we believe that our technique overestimated this resistance when there was marked frequency dependence. However, the excellent correlation coefficient for the regression line relating R_1 and Raw indicates that this forced random noise parameter provides a good measure of the overall resistive properties of the respiratory system and that it is sensitive to changes induced by bronchoconstriction. The parameter R_{5-9} also correlated well with Raw. However, when only the low-resistance data were considered, it was more difficult to explain the regression line than it was with R_1. The parameter R_{20-24} provided a poor measure of the overall resistive properties of the respiratory

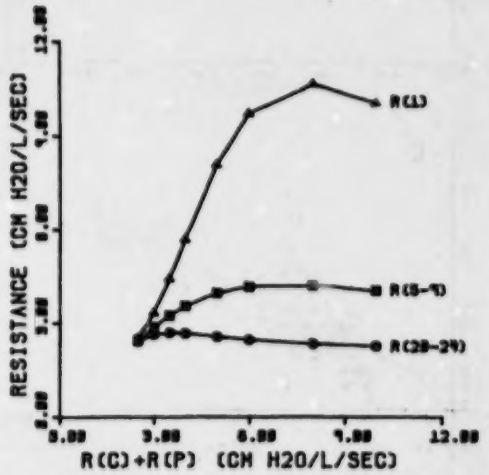

FIG. 7. Graphs showing R_1, R_{5-9}, and R_{20-24} as a function of Rc + Rp. Curves were derived from data in Fig. 6; these data were obtained by increasing Rp only.

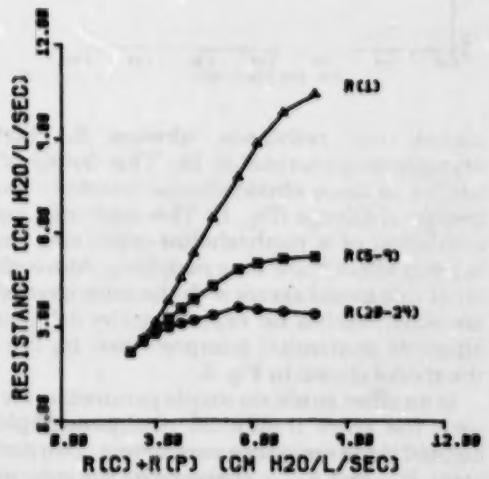

FIG. 8. Graphs showing R_1, R_{5-9}, and R_{20-24} as function of Rc + Rp. These curves were derived from data analogous to that shown in Fig. 6 except resistance increases were shared by Rc and Rp until Rc increased by 50% over nominal value.

system, and it was relatively insensitive to changes induced by bronchoconstriction.

The forced random noise technique provided data describing the frequency dependence of Rth. This relationship is thought to provide some measure of the degree of mechanical inhomogeneities in the lung. Thus the forced random noise technique provided information that was unobtainable by routine plethysmographic measurements. Plethysmography, of course, provides a measurement of thoracic gas volume which is not obtainable through forced oscillatory techniques (4).

In this study, methacholine increased the frequency-dependent behavior, and this index of response may be useful to monitor in bronchoconstrictive challenge studies. In an effort to quantify the degree of frequency dependence, the ratio of low- to high-frequency resistance has been used (7, 8). Such a ratio provides only indirect information about the distribution of resistance in the respiratory system. Algorithms that use this frequency dependence to estimate values for central and peripheral resistance parameters have been described (13, 14, 16). If these algorithms are valid and if the estimated "central" and "peripheral" resistance parameters correlate anatomically with the large and small airways, then the forced random noise technique would provide information that is not attainable in any other way.

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REFERENCES

1. DuBois, A. B., S. Y. Botelho, and J. H. Comroe, Jr. A new method for measuring airway resistance in man using a body plethysmograph: values in normal subjects and in patients with respiratory disease. *J. Clin. Invest.* 25: 327–335, 1956.
2. Eyles, J. G., and R. L. Pimmel. Evaluating lumped parameter models of respiratory mechanical behavior using the simplex algorithm. *Proc. Southeast Symp. System Theory 12th Virginia Beach VA 1980*, p. 223–227.
3. Finucane, I. E., S. V. Dawson, P. D. Phelan, and J. Mead. Resistance of intrathoracic airways of healthy subjects during periodic flow. *J. Appl. Physiol.* 38: 517–530, 1975.
4. Fisher, A. B., A. B. DuBois, and R. W. Hyde. Evaluation of the forced oscillation technique for the determination of resistance of breathing. *J. Clin. Invest.* 47: 2045–2057, 1968.
5. Fredberg, J. J., and J. Mead. Impedance of intrathoracic airway models during low frequency periodic flow. *J. Appl. Physiol.: Respirat. Environ. Exercise Physiol.* 47: 347–351, 1979.
6. Grimby, G., T. Takishima, W. Graham, P. Macklem, and J. Mead. Frequency dependence of flow resistance in patients with obstructive lung disease. *J. Clin. Invest.* 47: 1455–1465, 1968.
7. Hayes, D. A., R. L. Pimmel, J. M. Fullton, and P. A. Bromberg. Detection of respiratory mechanical dysfunction by forced random noise impedance parameters. *Am. Rev. Respir. Dis.* 120: 1245–1250, 1979.
8. Kjeldgaard, J. M., R. W. Hyde, D. M. Speers, and W. M. Reichert. Frequency dependence of total respiratory resistance in early airways disease. *Am. Rev. Respir. Dis.* 114: 501–508, 1976.
9. Mead, J. Contribution of compliance of airways to frequency-dependent behavior of lungs. *J. Appl. Physiol.* 26: 670–673, 1969.
10. Mead, J., and J. L. Whittenberger. Physical properties of human lungs measured during spontaneous respiration. *J. Appl. Physiol.* 5: 770–796, 1953.
11. Michaelson, E. D., E. D. Grassman, and W. R. Peters. Pulmonary mechanics by spectral analysis of forced random noise. *J. Clin. Invest.* 56: 1210–1230, 1975.
12. Otis, A. B., C. B. McKerrow, R. W. Bartlett, J. Mead, M. B. McIlroy, N. J. Selverstone, and E. P. Radford, Jr. Mechanical factors in distribution of pulmonary ventilation. *J. Appl. Physiol.* 8: 427–443, 1956.
13. Pimmel, R. L., M. J. Tsai, D. C. Winter, and P. A. Bromberg. Estimating central and peripheral respiratory resistance. *J. Appl. Physiol.: Respirat. Environ. Exercise Physiol.* 45: 375–380, 1978.
14. Slutsky, A. S., and J. M. Drazen. Estimating central and peripheral respiratory resistance: an alternative analysis. *J. Appl. Physiol.: Respirat. Environ. Exercise Physiol.* 47: 1325–1331, 1979.
15. Williams, S. P., J. M. Fullton, M. J. Tsai, R. L. Pimmel, and A. N. Collier. Respiratory impedance and derived parameters in young children by forced random noise. *J. Appl. Physiol.: Respirat. Environ. Exercise Physiol.* 47: 169–174, 1979.
16. Williams, S. P., R. L. Pimmel, J. M. Fullton, M. J. Tsai, and A. M. Collier. Fractionating respiratory resistance in young children. *J. Appl. Physiol.: Respirat. Environ. Exercise Physiol.* 47: 551–555, 1979.